

**The Problem:  
Non-Integrated Cancer  
Drug Development**

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Informative Non-Clinical  
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**Companion Animal  
Malignancies as  
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## Comparative Oncology Program

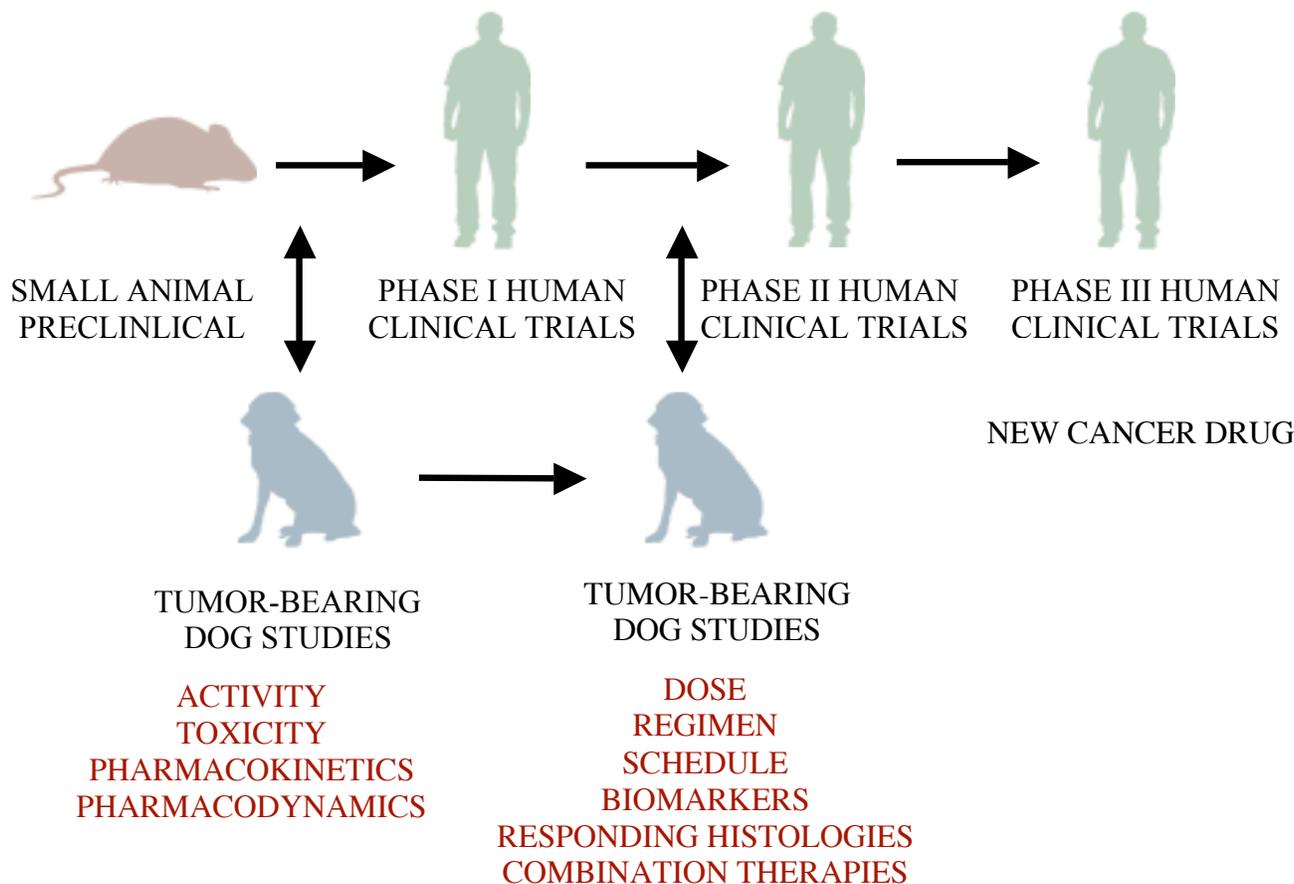
A central mission of the Center for Cancer Research (CCR), National Cancer Institute (NCI) is the development and delivery of novel cancer treatment strategies to patients. Through a number of new initiatives, the CCR has created an essential infrastructure to improve the translational research process. As part of these efforts, the CCR recently launched the CCR–Comparative Oncology Program (CCR-COP). The goal of this program is to include naturally occurring cancers seen in pet animals into studies of cancer biology and therapy. Through the inclusion of these non-murine cancer models, we are hopeful that a more efficient and informed drug development path may emerge.

### The Problem: Non-Integrated Cancer Drug Development

Cancer drug development is costly, linear, and inefficient. Costs associated with development incrementally rise as the path proceeds. The two most common causes of drug failure are toxicity or lack of efficacy. These failures are most costly once a drug enters phase I human trials but are even more costly if they occur after phase II trials, and beyond. It is therefore essential that “go-no-go” decisions focus on the issue of toxicity and efficacy as early in the development path as possible. Many problems, which result from a lack of integration between those involved with “drug discovery” and those involved with “drug development,” limit the information needed to answer important questions faced in the design of clinical trials in human patients.

An information gap has historically existed between preclinical studies and phase I human trials; however, with the development of novel non-cytotoxic anti-cancer agents, this gap is now equally evident later in the drug development path. After successful completion of phase I human clinical trials, the design of phase II trials often has to take place without sufficient information including biological dose, schedule, and regimen for many of these novel agents. To a large extent, the lack of relevant preclinical animal models of cancer (i.e., the mouse) or their inappropriate use can be blamed for the lack of efforts to integrate drug discovery and drug development groups and provide the information needed to more efficiently move new drugs through the development process. For cytotoxic chemotherapy, it is likely that some of these questions may be answered through murine xenograft cancer models that include consideration of pharmacological and pharmacokinetic endpoints. However, for both cytotoxic and, more importantly novel non-cytotoxic agents, additional model systems are needed.

## A Solution: Integration of Informative Non-Clinical Models of Cancer With Clinical Drug Development



An under-utilized group of non-clinical animal models for cancer drug development includes companion animals, primarily dogs, that develop naturally occurring malignancies. These animal models are optimal for the integration of drug discovery and development efforts. In the United States, there are approximately 60 million pet dogs. Based on crude incidence rates, it is estimated there are over 4 million new cases of cancer diagnosed in pet dogs each year. The pet owning population is motivated to seek out new and effective treatment options for their pet animals with cancer. This includes participation in clinical trials of investigational anti-cancer agents.

By their nature, companion animal cancers are characterized by inter-patient and intra-tumoral heterogeneity, the development of recurrent or resistant disease, and metastasis to relevant distant sites. In these ways, companion animal cancers capture the “essence” of the problem of cancer in ways not seen in other animal model systems. The lack of gold standard treatments for canine cancer patients allows for the early and humane testing of novel therapies. The shortened life span of companion animal patients and their early metastatic failure allow rapid completion of clinical trials. A further rationale for the use of these models in non-clinical efficacy studies is the immune competence of the host, relevant and species-concordant tumor-microenvironment interactions, spontaneous development of tumors, and more importantly spontaneous development of resistance patterns within an individual animal. Studies in companion animals can allow serial biopsies from target and non-target lesions, and repeated body fluid collection (serum, whole blood, urine) from the same animal during exposure to an investigational agent. These advantages are currently being applied to the development of novel cytotoxic and biology-based anticancer drugs, and to the identification and validation of biological endpoints and surrogate markers critical to the design of phase I and phase II human clinical trials.

These “model” advantages of companion animal cancers provide an opportunity to integrate studies that include companion animals into the development paths of new cancer drugs. The outcome will include earlier assessment of agent activity and toxicity (for Go-No-Go decisions), and the identification and validation of biological endpoints and surrogate markers critical to the design of phase I and phase II human clinical trials.

## Companion Animal Malignancies as a Comparative Model for Human Disease

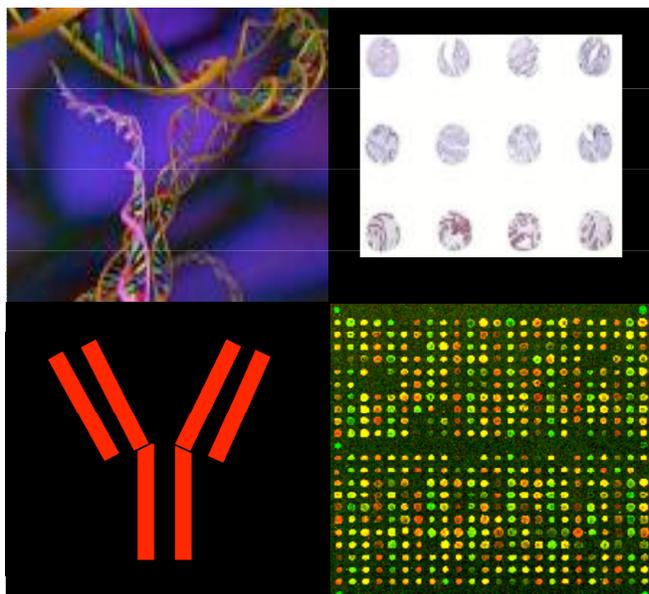
The value of naturally occurring cancers seen in companion animals, as models of human cancer has been recognized for over 30 years. Early studies in the field of bone marrow transplantation utilized dogs with non-Hodgkin's lymphoma to define optimal preparatory regimens for bone marrow transplant. Since then, the activity and optimal use of a wide variety of anticancer agents have benefited from information derived from studies in these large animal models. A recognized and long standing weakness of these models was a limited opportunity to investigate the biological basis of an anticancer agent's activity or lack of activity.

Through the release of the canine genome sequence, reductions in the cost of generating biological reagents, and continued efforts by academic researchers, biological reagents that can answer questions of drug-tumor biology in dogs are increasingly available. Evidence of this includes the availability of a canine oligonucleotide microarray, optimized conditions for proteomics studies using conventional chip technology, and validated canine specific and human antibodies that cross react with canine epitopes. The momentum in the field has resulted in the inclusion of comparative oncology efforts within several NCI sanctioned comprehensive cancer centers, the use of dogs with cancer in efficacy studies sponsored by the pharmaceutical industry, and the announcement of the NCI Center for Cancer Research–Comparative Oncology Program (CCR-COP).

The CCR-COP is uniquely positioned to minimize the hurdles associated with cancer drug development through the integration of non-clinical studies in companion dogs to inform the design and implementation of human clinical trials. A primary effort of the CCR-COP is the development of a “biological reagent kit” that continues to enhance the transfer of clinical and biological information from dog trials to human trials.

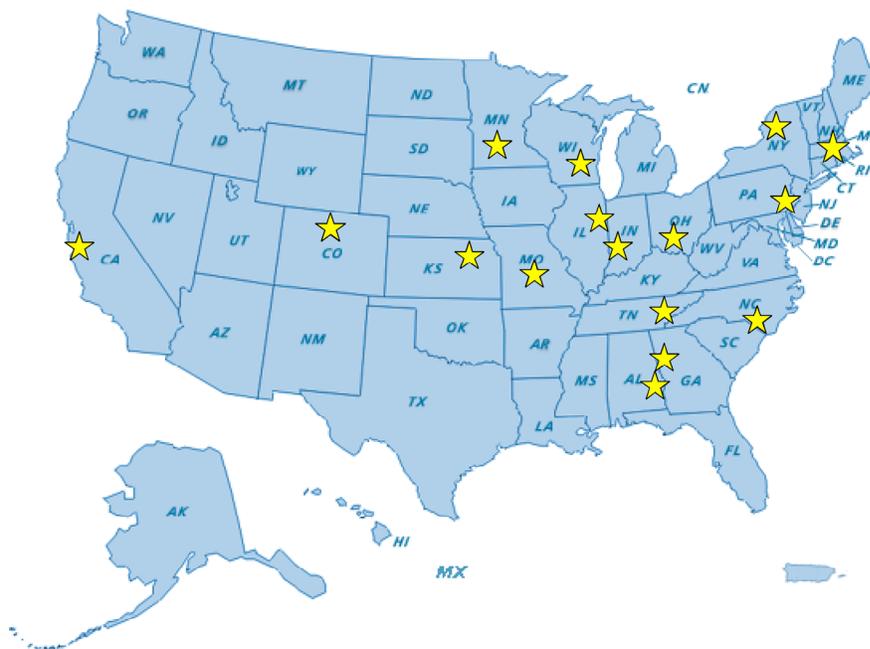
## Comparative Oncology Program Reagent Kit

- Annotation and Use of Canine Oligonucleotide Microarray
  - Quality and assurance testing of a robust canine oligonucleotide microarray is completed
  - Studies to define expression profiles of canine cancers is underway
- Optimized Protocols for Proteomic Studies in Dogs
  - Serum profiling of canine prostate cancer patients is ongoing
- Validated Cross Reacting Antibody Database
  - Validation of human antibodies that cross react with canine tissues is in progress



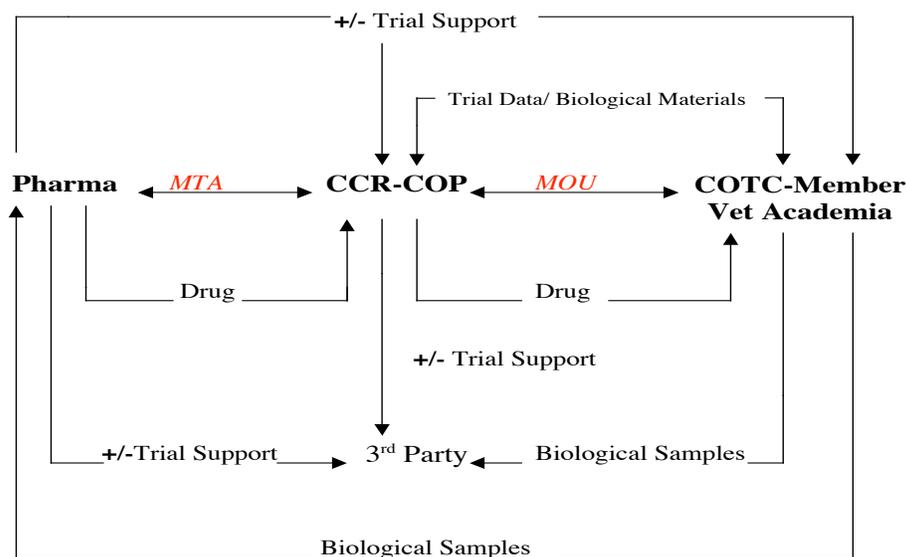
## Comparative Oncology Trial Consortium

In an effort to establish the organizational infrastructure to undertake translational clinical trials in companion animals, the CCR-COP has formed the **Comparative Oncology Trial Consortium (COTC)**. This new drug development consortium is based on collaborative relationships with accredited schools of veterinary medicine. The COTC will initiate trials in collaboration with NCI investigators, academic institutions, and the pharmaceutical industry. These trials will be implemented through the collective caseloads of the COTC membership institutions with trial design, oversight, data management, and assessment of biological endpoints organized by the CCR-COP. These trials will be small in scale and will emphasize the assessment of biological questions related to drug development. The design of these trials will answer essential questions emerging from the development plans of agents destined for human patients.



## Organizational Structure of the COTC

In order to streamline this process, the CCR-COP has developed template agreements that will allow the rapid transfer of therapeutic agents from providers—primarily, interested pharmaceutical companies—to the CCR-COP and the COTC. The Materials Transfer Agreement (MTA) between the CCR-COP and sponsors of investigational agents are based on an agreed Memorandum of Understanding (MOU) between the CCR-COP and the veterinary academic institutions. In this way, the CCR-COP can negotiate a single MTA on behalf of all COTC members.



## Frequently Asked Questions

### **What specifically does the MOU entail?**

The MOU defines terms of agreement that will allow the CCR-COP to negotiate with members of the pharmaceutical industry or the intramural NCI for the transfer of reagents and support that will be used in the conduct of each specific non-clinical study. Institutional acceptance and signage of this MOU defines membership within the COTC.

### **What are the defining details of the MTA?**

This MTA will delineate the terms of agreement that will allow the CCR-COP to receive investigational agents and redistribute these agents to the COTC members who will conduct the non-clinical trial. The terms of agreement outlined in this MTA are similar to those used in the COTC MOU.

### **Have issues of intellectual property, licensing and confidentiality been addressed by the COTC?**

Information relating to the intellectual property, licensing opportunities, and confidentiality have been agreed upon by all COTC participants and are defined in the COTC MTA and MOU.

### **What if a COTC member does not wish to be a part of a particular non-clinical trial?**

Institutions will have the right to decline participation in any COTC non-clinical trial. This right may be exercised at any time.

### **How will clinical trials be designed and implemented within the CCR-COP framework?**

The conceptualization of a non-clinical trial, conducted in companion animals may come from the pharmaceutical company provider, the CCR-COP, or members of the COTC. The design and implementation of the trial will be coordinated through the CCR-COP, COTC members, and the Provider. This effort will result in a brief Trial Overview that will define the priorities of the non-clinical trials and outline responsibilities for all participants. The Trial Overview will be reviewed and prioritized by the COP based on the ability to enhance the development plans of the therapeutic agent in question. A favorably reviewed Trial Overview will be used to draft a more formal Trial Protocol and the necessary trial agreements (MTA).

## Summary

Recent interest by the Food and Drug Administration in the use of data from pre-clinical companion animal trials as part of the evaluation of novel anti-cancer therapeutics further reinforces the value of the integration of companion animal studies into drug development paths. The formation of the COTC will provide members of the pharmaceutical industry and academic community with the opportunity to work together and realize the benefits provided by a comparative approach towards studies of cancer biology and therapy. Implications of this approach may allow for the re-emergence of agents previously considered to be ineffective, the opportunity to understand the reasons that some clinical trials have failed, and to move new agents through conventional development paths with greater information and confidence.

The CCR-Comparative Oncology Program welcomes interest in the study of new cancer agents in companion animals and the newly formed Comparative Oncology Trials Consortium.



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